Cordis Presentation

Cordis Radiation System
(CHECKMATE™)

PMA #P990036

Agenda

- Overview - Dennis Donohoe, M.D.
  Vice President, Clinical Research
  - Project overview

The Problem of In-Stent Restenosis

- No effective therapies available
- Large growing patient population
  - Experience frequent, recurrent admissions
- Pathology: Intimal hyperplasia

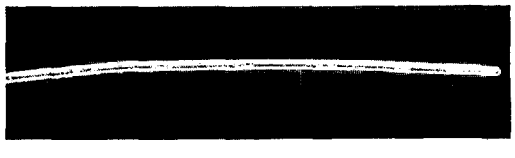
Use of Radiation Therapy

- Brachytherapy has been used for about 100 years in treatment of malignancies
- There is a sizable body of knowledge
  - Handling of radioactive sources
  - Clinical response of tissue to implants
  - Treatment of benign hyperproliferative lesions
- In-stent restenosis is a benign hyperproliferative process

Selection of Gamma Radiation

- Iridium 192 (Ir-192) is a gamma-emitter which provides desired dose distribution
- NRC registered source for past 40 years
- Provides satisfactory safety margin for dwell-time (average dwell 20 minutes)
- Presence of calcification and metallic stent struts within the arterial wall does not alter the dose distribution
- Extensive experience by radiation oncologists and physicists in the use of gamma radiation

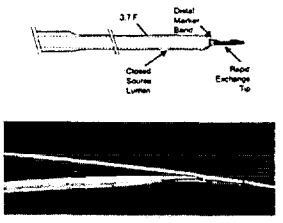
Source Ribbons

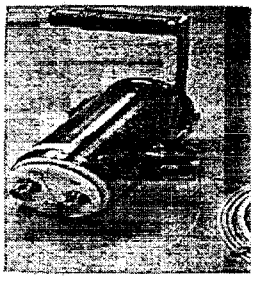


Treatment Lengths:

No. of Seeds	Lesion Length
6 Seeds	≤ 15 mm
10 Seeds	> 15 mm to ≤ 30 mm
14 Seeds	> 30 mm to ≤ 45 mm

Cordis Catheter and Delivery Device





Simple Delivery

Radiation Procedure

- Perform routine angioplasty procedure with IVUS
- Insert catheter with dummy ribbon
  - Position across treatment site
  - Confirm placement (cardiologist and radiation oncologist)
  - Calculate dwell time (physicist and radiation oncologist)
- Exchange dummy ribbon for active source ribbon
- Remove active source ribbon

Team Approach

- Radiation oncologist
- Medical physicist
- Interventional cardiologist
- Radiation safety officer

Project Overview

- Submitted PMA on June 30, 1999
- Granted expedited review status
  - **No alternative therapies**
- PMA Contents
  - Three randomized, double-blind, placebo controlled trials
  - Overwhelming efficacy
  - Durability of treatment

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Project Overview (cont.)

- Safety profile issues
  - Thoroughly investigated by Cordis
  - Late total occlusion and late thrombosis
    - Associated with new stent placement
    - Short duration antiplatelet therapy

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Project Overview (cont.)

- Risk/Benefit Ratio
  - Overwhelming efficacy in difficult patient population with no alternative therapies
  - Manageable risk by:
    - avoiding new stent use
    - providing extended antiplatelet therapy

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Agenda

- Overview - Dennis Donohoe, M.D.
  - Project overview
- Clinical results - David Holmes, M.D.
  - Safety and efficacy results of three randomized trials
- Specific clinical issues - Richard Kuntz, M.D., M.Sc.
  - Late total occlusion and late thrombosis
- Conclusions - David Holmes, M.D.

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Clinical Results

David R. Holmes, Jr., M.D.
Director of Cardiac Catheterization Lab
Professor of Medicine
Mayo Clinic
Rochester, Minnesota

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Financial Disclosure

- Honorarium
- Travel Expenses

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In-Stent Restenosis

- Mechanism and Frequency
  - 1999: 750,000 PTCAs, 75% stent
  - 20% in-stent restenosis
  - Frequency will increase with greater stent use in smaller vessels, more diffuse disease
  - **Over 100,000 patients with in-stent restenosis annually in USA**
  - Excessive neointimal hyperplasia

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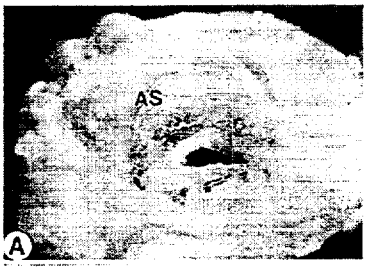
In-Stent Restenosis Neointima Hyperplasia Restenosis in Human LAD



(Komatsu et. al. Circ. 98(3), 224 (1998))

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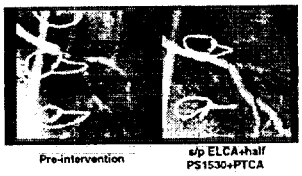
In-Stent Restenosis

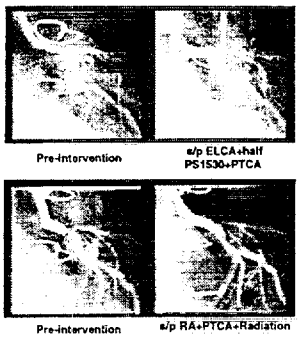
- 42 year old attorney
  - 10K runner, developed angina, critical left main disease
- 11/92 CABG
  - LIMA to LAD
  - SVG to Cx
- 6/95 Patent LIMA
  - PS1530 implanted ostial Cx
- 9/95 1st in-stent restenosis
  - PTCA



- 10/95 2nd in-stent restenosis
  - ELCA
  - PTCA

In-Stent Restenosis

- 1/96 3rd in-stent restenosis
  - ELCA
  - PS1530 stent
- 7/96 4th in-stent restenosis
  - PTCA
  - PS1530 stent
- 2/97 5th in-stent restenosis
  - RA
  - PTCA
  - Ir-192



Representative Patient with Recurrent In-Stent Restenosis

What Are The Issues?

- Already has had one surgical procedure
- LIMA excellent
- Recurrent angina from recurrent in-stent restenosis despite medical therapy and multiple interventions including stent implantation, rotational atherectomy, laser and PTCA

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In-Stent Restenosis

- Factors associated with in-stent restenosis
  - Vessel diameter, lesion length, diabetes and LAD location
- Existing treatment options
  - PTCA, rotational atherectomy, laser, re-stenting, or combination
  - Re-recurrence rate approximately 50% (19-85%)

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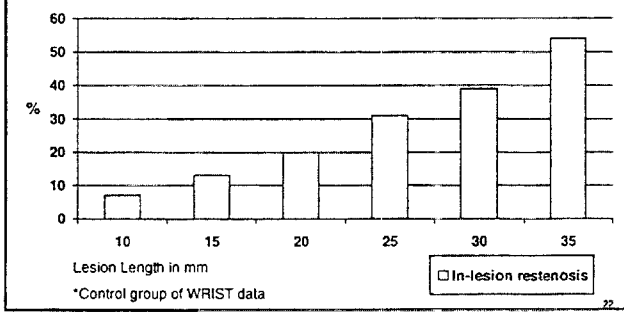
*Influence of Lesion Length on Restenosis Rates**



*Control group of WRIST data

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Clinical Trials

- Three randomized, placebo-controlled, double-blind trials conducted with Ir-192 Radiation System
- Independent DSMB, angiographic core lab, data management and clinical events adjudication for all studies

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The Evolution of the Clinical Trials

SCRIPPS I - single site, 60 patients, initiated 3/95

WRIST - single site, 130 patients, initiated 2/97

GAMMA I - 12 sites, 252 patients, initiated 12/97

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Design of Trials

	SCRIPPS I	WRIST	GAMMA I
Randomized	Yes	Yes	Yes
Inclusions	In-stent/POBA Restenosis	In-stent Restenosis	In-stent Restenosis
Source	Ir-192	Ir-192	Ir-192
Native vessel vs. SVG %	73%	77%	98%

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Design of Trials (cont.)

	SCRIPPS I	WRIST	GAMMA I
Crossover	Yes	Yes	No
Dosimetry	IVUS	Fixed	IVUS
Dose	800-3000 cGy	1500 cGy at 2 mm	800-3000 cGy
Antiplatelet Therapy	2 weeks	4 weeks	8 weeks

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Key Clinical Demographic Variables

Variables	SCRIPPS I	WRIST	GAMMA I
Diabetics	35.7%	41.9%	31.3%
LAD	33.3%	26.4%	39.0%
CCS Class III/IV	81.0%	75.0%	69.4%
Prior Procedures to Target ($\bar{X}\pm SD$) range	1.9±1.1 up to 6	1.6±0.8 up to 6	1.7±1.2 up to 12

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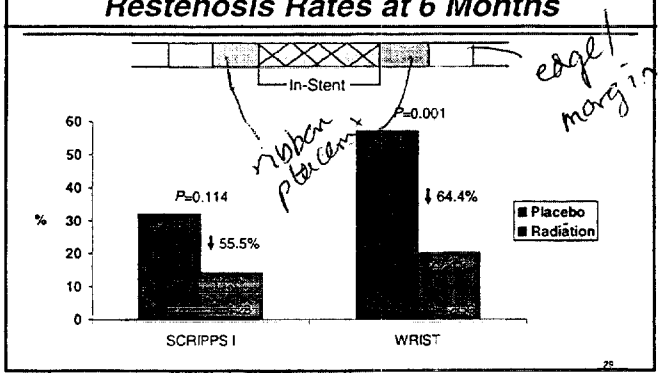
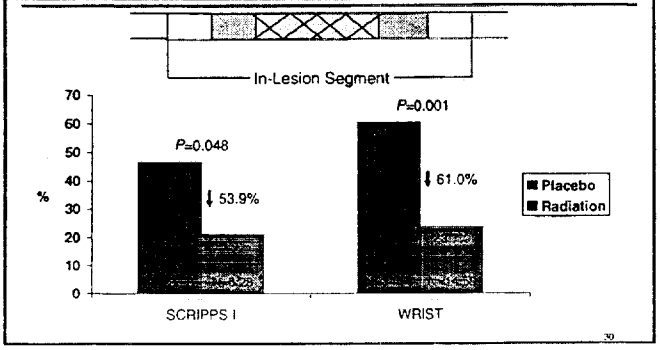
Key Angiographic Demographic Variables

Variables	SCRIPPS I	WRIST	GAMMA I
Lesion Lgth ($\bar{X}$±SD)	12.63±7.38	20.37±10.47	19.62±10.15
range (mm)	2.70-37.44	3.52-67.50	2.00-59.24
RVD ($\bar{X}$±SD)	2.79±0.53	2.72±0.54	2.71±0.51
range (mm)	1.51-4.58	1.70-4.68	1.37-4.49

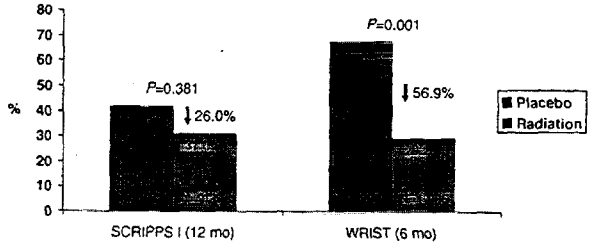
SCRIPPS I and WRIST: In-Stent Restenosis Rates at 6 Months



SCRIPPS I and WRIST: In-Lesion Restenosis Rates at 6 Months



SCRIPPS I and WRIST: MACE Events



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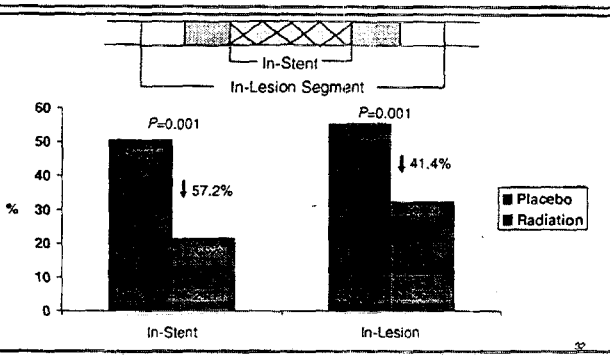
* & cohort of pts who experience a MACE

GAMMA I: In-Stent and In-Lesion Restenosis Rates at 6 Months



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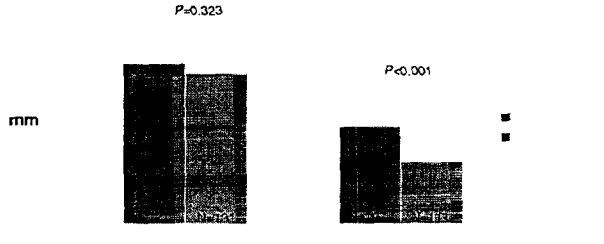
GAMMA I: 6-Month Follow Up Lesion Length



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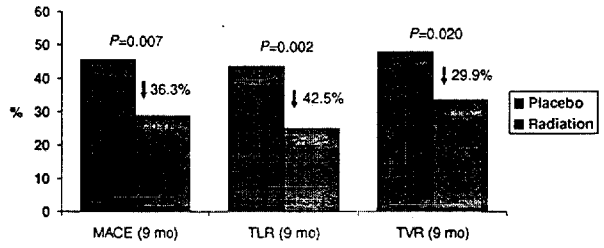
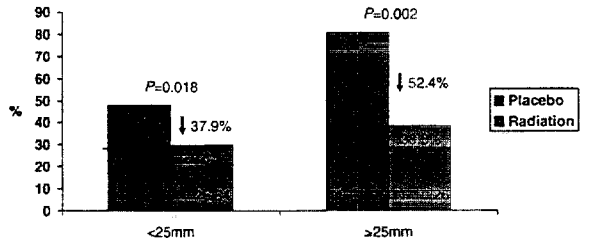
* for pts who failed tx, what was new (recurrent) lesion size?

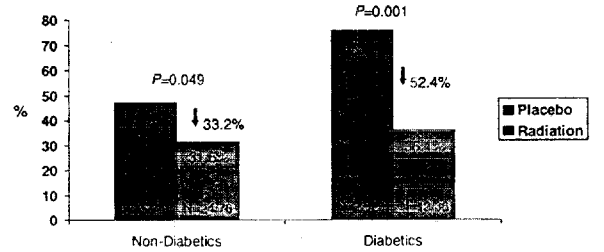
GAMMA I: MACE Events, TLR and TVR



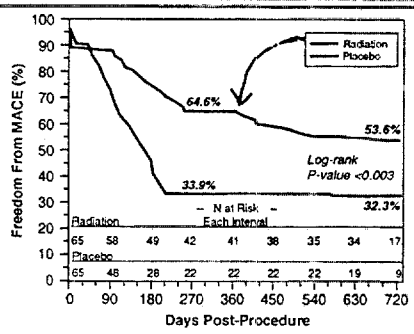
GAMMA I: Influence of Lesion Length on In-Lesion Restenosis



GAMMA I: Influence of Diabetes on In-Lesion Restenosis Rates

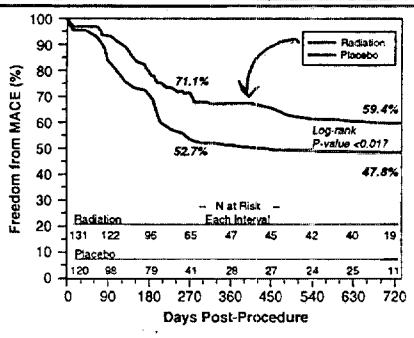


WRIST: Freedom From MACE at 2 Years



flat, because patients crossed over

GAMMA I: MACE-Free Survival at 2 Years



Clinical Trials Efficacy Summary

- Benefits
  - Concordant efficacy in 3 studies; angiographic and clinical
  - Effective across wide range of patient populations (diabetics, longer lesions)
  - Durability of efficacy
    - 3 year SCRIPPS I
    - 2 year WRIST
    - 2 year GAMMA I

Clinical Trials Safety Summary

- Deaths
  - Underlying causes
- Myocardial infarctions
  - Associated with late thrombosis
- Long-term safety
- Radiation safety

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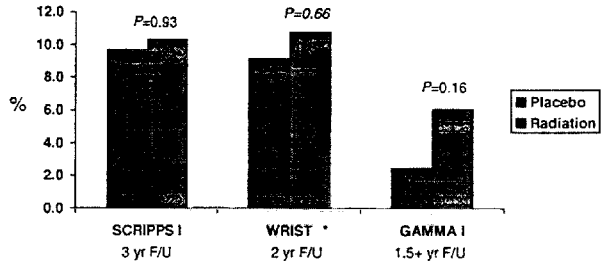
Summary of All Deaths Intention to Treat Analysis



*WRIST Placebo rate excluding crossover is 7.7% (2/26). *P*=0.66

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GAMMA I: Summary of Deaths

	Placebo	Radiation
Non-cardiac	---	0.8% (1/131, suicide)
Post-procedural	---	0.8% (1/131, guidewire perforation)
Non-procedural cardiac	2.5% (3/121)	4.6% (6/131)

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GAMMA I: Deaths in Radiation Group

- Pt 6/4: At day 153 had PTCA for target lesion restenosis, not thrombosis. At day 256 had target lesion restenosis plus 3 vessel disease. Scheduled for CABG but six days later had Q-wave MI, shock leading to death.
- Pt 118/15: At 3 months admitted with unstable angina, no MI. Angiogram found target lesion restenosis with thrombus. Successful PTCA, Vfib arrest 4 days later.

GAMMA I: Deaths in Radiation Group (cont.)

- Pt 11/12: At day 173 had PTCA for target lesion restenosis, not thrombosis. At day 291 had non-Q wave MI, angio found "diffuse disease" but no target lesion restenosis or thrombosis. Angiogram complicated by shock, CHF, and renal failure leading to death on day 293.
- Pt 11/29: At day 135 had PTCA for target lesion restenosis, not thrombosis. At day 675 had sudden death at home.

GAMMA I: Deaths in Radiation Group (cont.)

- Pt 11/14: At day 67 had Q wave MI. Angio found occluded vessel due to late thrombosis successfully treated with PTCA. At day 265 had CABG. At day 690 had death due to CHF.
- Pt 7/6: At day 181 had PTCA for target lesion restenosis, not thrombosis. At day 311 went to hospital with SOB. In radiology during CXR had sudden death. Autopsy showed pulmonary edema, no MI.

GAMMA I: Deaths in Placebo Group

- Pt 39/7: At six-month angio no restenosis. At 618 days death of unknown cause.
- Pt 11/22: At day 78 had CABG for target lesion restenosis. At day 175 had PTCA. At day 485 had TMR, complicated by VT/VF and death.
- Pt 6/5: At 3 months had target lesion restenosis, not thrombosis, treated with CABG, post-op had VT/VF arrest.

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Clinical Impact of Late Thrombosis

- Definition of Late Thrombosis
  - Myocardial infarction attributable to the target vessel with angiographic documentation (site reported or by QCA) of thrombus or total occlusion at the target site ≥31 days from the index procedure in absence of intervening revascularization of target vessel

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GAMMA I: Deaths Possibly Associated with Late Thrombosis

- One placebo patient (39/7) and one radiation treated (11/29) patient have insufficient information to definitely exclude the possibility of an association with late thrombosis
- One death in the radiation group was possibly associated with late thrombosis. Pt118/15: Angiogram found target lesion restenosis with thrombus. Successful PTCA, Vfib arrest 4 days later

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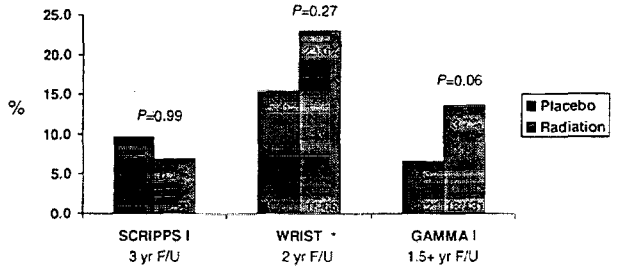
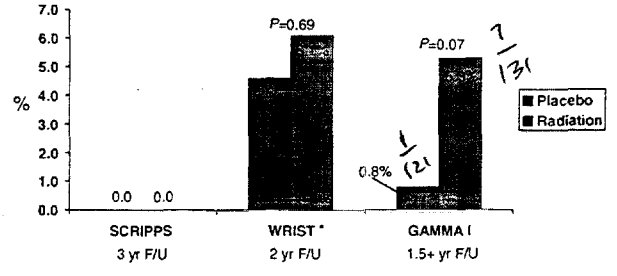
Summary of all Patients with Myocardial Infarctions



*WRIST Placebo MI rate excluding crossover is 23.0% (6/26, p=0.99)

Summary of MI's Associated with Late Thrombosis



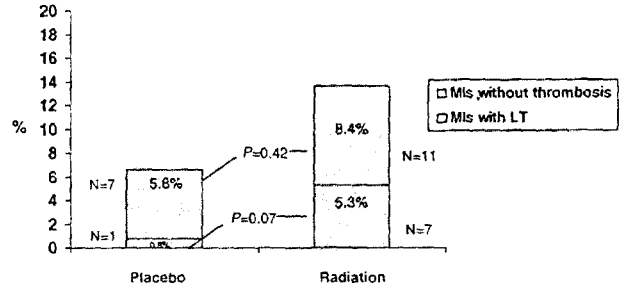
*WRIST placebo MI with late thrombosis rate excluding crossover is 3.9% (1/26), P=0.99

1/121 vs. 7/131 (Gamma)

GAMMA I: Summary of Late Thrombosis in Radiation Treated Patients

	Days to Event	Antiplatelet Days	MI	New Stent
1	95	61	Q	Yes
2	135	47+	Q	Yes
3	67	25+	Non-Q	Yes
4	72	62	Non-Q	Yes
5	101	63	Non-Q	Yes
6	128	55	Non-Q	Yes
7	270	62	Non-Q	Yes

GAMMA I: Myocardial Infarction Impact of Late Thrombosis



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SCRIPPS I: Long-Term Safety

- Three-year angiographic follow-up radiation treated patients
  - No aneurysms
  - No pseudoaneurysms
  - No perforations

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Safety of the Cordis Radiation System

- In over 1000 patients treated to date
  - No device failures (Ir-192 ribbons were delivered 100% of the time)
  - No NRC reportable events
  - No procedures aborted or bailout box/ bailout pig used

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Clinical Trials Safety Summary

- One death in radiation group was possibly associated with late thrombosis
- There is an overall higher rate of MIs in the radiation group because of the occurrence of late thrombosis
- Myocardial infarctions unrelated to late thrombosis occur at comparable rates

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Specific Clinical Issues

Richard E. Kuntz, M.D., M.Sc.
Chief, Clinical Biometrics Division
Brigham & Women's Hospital/Harvard Medical School
Boston, MA

Financial Disclosure

- None

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Occlusions and Late Thrombosis Analysis

- Definitions
- Examination of GAMMA I Trial
- Examination of pooled data from three trials
- Role of antiplatelet therapy

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Occlusions and Late Thrombosis Analysis

- **Late total occlusion - definition**
- **Late thrombosis and total occlusion definitions**
  - **Dissimilar endpoints**
  - **Late thrombosis is the most specific endpoint**
- Examination of GAMMA I Trial
- Examination of pooled data from three trials
- Role of antiplatelet therapy

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Late Total Occlusion Definition

- Late Total Occlusion - A composite of two events
  - Late Thrombosis - Present with MI with angiographic documentation of thrombus or total occlusion at the target vessel ≥31 days from index procedure in absence of intervening revascularization of target vessel
  - Total (Silent) Occlusion - Angiographic documentation of 100% stenosis of target site without MI at ≥31 days from index procedure

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Late Total Occlusion Mechanisms of Action

- Late Thrombosis
  - Fresh thrombus formation
  - Possibly due to inhibition of neointima formation
- Total (Silent) Occlusion
  - Progressive disease
  - Excessive neointima formation
  - Possible contribution from thrombus formation

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Late Total Occlusion - All Trials

- CDAC re-adjudicated all events in GAMMA I, SCRIPPS I, and WRIST using same definitions for:
  - Late thrombosis
  - Total (silent) occlusion

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Occlusions and Late Thrombosis Analysis

- Definitions
- **Examination of GAMMA I Trial**
- Examination of pooled data from three trials
- Role of antiplatelet therapy

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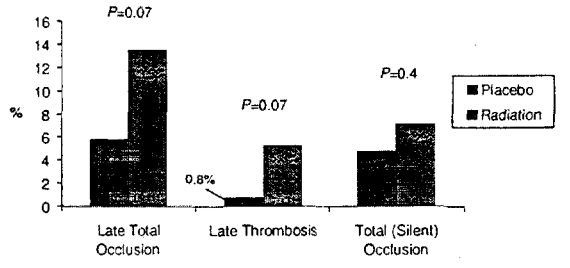
GAMMA I Results (Clinical) Late Total Occlusions



This is one component of MACE, teased out

GAMMA I: Multivariate Analysis

- Multivariable determinants in GAMMA I for late thrombosis and late (silent) occlusions
  - Assessed multiple parameters including lesion length, minimum luminal diameter post-procedure, presence of new stent, treatment assignment, dose, and reference vessel diameter
  - No significant predictors

Occlusions and Late Thrombosis Analysis

- Definitions
- Examination of GAMMA I Trial
- **Examination of pooled data from three trials**
- Role of antiplatelet therapy

Pooling Motivation

- Increase statistical power to evaluate the determinants of late thrombosis
  - Late thrombosis is a relatively rare event
- Pooling not motivated for proving efficacy
  - The three trials stand on their own

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Pooling Justification

- Equivalent inclusion and exclusion criteria
- Equivalent treatment (Ir-192)
  - Overlapping range of dosimetry
- Statistical analysis of patients in all three trials justifies pooling despite different dosimetry protocols

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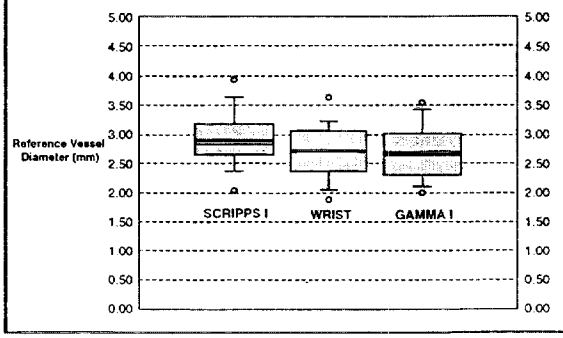
Reference Vessel Diameter for All 3 Trials



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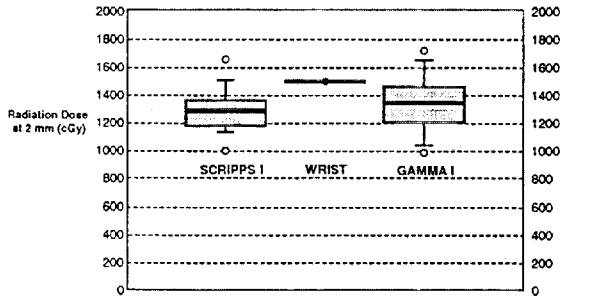
±25%, median, mean
whiskers indicate
outliers

Radiation Dose at 2 mm From the Source for All Three Trials



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Treatment Assignment

	PLACEBO		RADIATION	
	New Stent	No New Stent	New Stent	No New Stent
SCRIPPS I	23	8	21	8
WRIST (Randomized)	20	45	27	38
WRIST (Crossover)	--	--	21	18
GAMMA I	102	19	111	20
Totals	**145**	**72**	**180**	**84**

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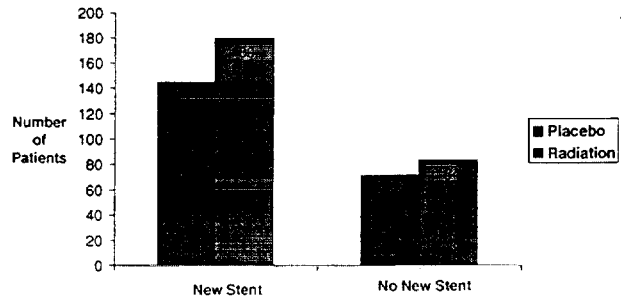
Distribution of Radiation Therapy and New Stent Use (Pooled Data)



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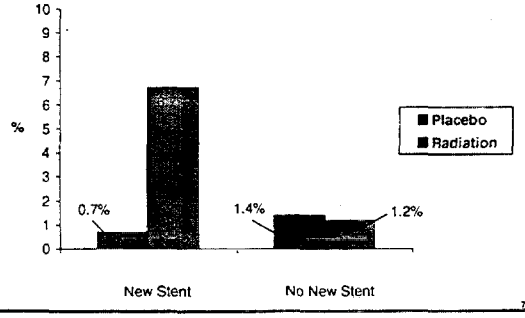
Late Thrombosis by Treatment Assignment

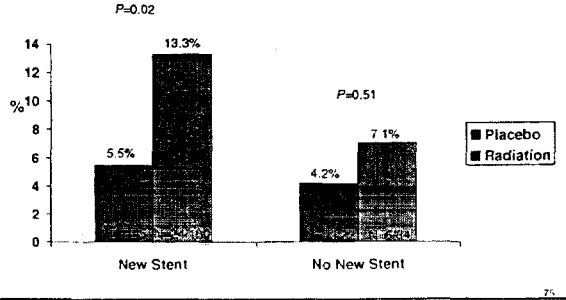
	PLACEBO				RADIATION			
	New Stent		No New Stent		New Stent		No New Stent	
SCRIPPS I	0.0%	(0/23)	0.0%	(0/8)	0.0%	(0/21)	0.0%	(0/8)
WRIST	5.0%	(1/20)	0.0%	(0/45)	11.1%	(3/27)	2.6%	(1/38)
WRIST (Crossover)	--		--		9.5%	(2/21)	0.0%	(0/18)
GAMMA I	0.0%	(0/102)	5.3%	(1/19)	6.3%	(7/111)	0.0%	(0/20)
Total	**0.7%**	**(1/145)**	**1.4%**	**(1/72)**	**6.7%**	**(12/180)**	**1.2%**	**(1/84)**

1% typical, ~~8~~

Distribution of Late Thrombosis (Pooled Data)



Late Total Occlusion - Pooled Data



Multivariable Determinants of Late Thrombosis and Total (Silent) Occlusion (Pooled Data)

- Late thrombosis determined by:
  - Radiation with new stent use, *P*=0.007
  - Lesion length, *P*=0.003
- Total (silent) occlusion determined by:
  - Pre-procedural RVD, *P*=0.038

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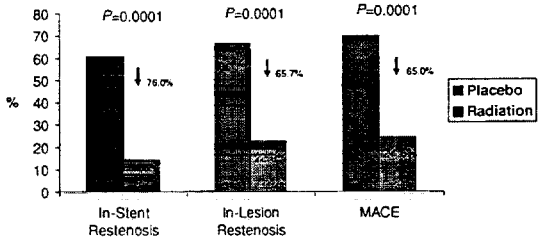
Native Coronary Arteries Without New Stent Placement Efficacy Results (Pooled Data)



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* pooled across studies

Prevention of Late Thrombosis Based on Pooled Data

- Pooled data from the three trials identified factors associated with late thrombosis and allow the hypothesis to be generated that late thrombosis would be prevented with avoidance of new stent placement in conjunction with radiation
- Efficacy of anti-restenosis effect of radiation treatment is preserved without new stent placement

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Occlusions and Late Thrombosis Analysis

- Definitions
- Examination of GAMMA I Trial
- Examination of pooled data from three trials
- **Role of antiplatelet therapy in the prevention of late thrombosis using prospective data**
  - **SCRIPPS III Registry**
  - **WRIST Plus Registry**

SCRIPPS III and WRIST Plus: Study Design

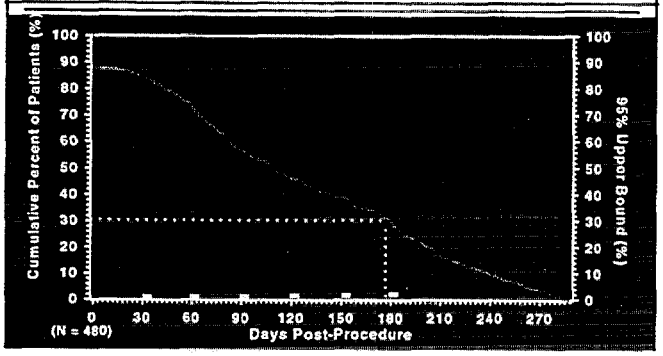
	SCRIPPS III	WRIST Plus
Type trial	Registry	Registry
# of Patients	360 (ongoing)	120
# of Sites	2	1
Vessels	Native & SVG	Native & SVG
% New Stent Use	25.7%	29.2%
Dosimetry	Fixed 1400 cGy	Fixed 1400 cGy
Antiplatelet	6 Months All Pts*	6 Months All Pts

*Changed to 6 months no new stent and 12 month with new stent

SCRIPPS III and WRIST Plus: Summary of Late Thrombosis Events

Follow-up Days	Number of Patients	LT Rate	95% Upper Bound
30	390	0%	0.8%
60	343	0%	0.9%
90	266	0%	1.1%
120	203	0%	1.5%
150	181	0%	1.6%
180	**140**	**0%**	**2.1%**
210	78	0%	3.8%

SCRIPPS III and WRIST Plus: Probability of LT Events



All pts, ranked by duration of follow up

What Have We Learned?

- Late thrombosis is predictable
  - New stent use with radiation
  - Lack of antiplatelet coverage

Late Thrombosis Conclusions

- Rate of late thrombosis for radiation without new stent placement is comparable to placebo
- Late thrombosis is largely confined to patients who received a new stent at time of radiation therapy
- Extended antiplatelet therapy prevents late thrombosis

Closing Remarks

David R. Holmes, Jr., M.D.
Director of Cardiac Catheterization Lab
Professor of Medicine
Mayo Clinic
Rochester, Minnesota

Closing Remarks

- In-stent restenosis patient population
  - Major clinical need
  - **No other alternative therapies**
- PMA supported by three randomized, double-blind, controlled trials

Efficacy Conclusions

- Marked and concordant efficacy demonstrated in all three trials
- Efficacy demonstrated in high-risk patients
- Efficacy maintained with or without new stent use
- Durability of efficacy demonstrated over two to three year follow-up

Safety Conclusions

- Cordis System has been demonstrated to be a safe and easy system to use
- Device
  - 1000 procedures performed without bailout or reportable event
- Long-term safety
  - Three year angiographic follow up: No radiation injury to vessels

Safety Issues Identified

- Late thrombosis
  - Unanticipated event for GAMMA I trial
  - Discovered through initial adjudication process during the follow up
  - Resulted in creating and modifying the late thrombosis definition to better understand the event
  - Conducted in-depth analysis of late thrombosis event

Results of Late Thrombosis Analysis

- Late thrombosis occurs with
  - New stent and radiation treatment
  - Short course of antiplatelet therapy
- Late thrombosis is preventable
  - Avoid new stent use
  - Extend antiplatelet therapy
  - Validated by recent trials
    - SCRIPPS III
    - WRIST Plus

Conclusions

- Appropriate to manage risk through:
  - Label warning
  - Physician training program
  - Providing updated information through post-market surveillance
- Risk/Benefit Ratio
  - Informed physician/patient decision

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Patient Outcome

- 8/97 6 month post radiation therapy

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